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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,200	03/22/2006	Se Hwan Yang	58049-00025	4449

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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	
MAIL DATE	DELIVERY MODE
09/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,200	YANG ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,10,11 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,11 and 13* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/3/09 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 7/3/09 is acknowledged. Claims 2-7, 9, 12 and 14-17 are cancelled. Claim 1 is amended. Claims 1, 8, 10, 11 and 13 are pending in this application and under examination in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this office action, has been overcome by Applicant's response.

4. Applicant's arguments filed on 7/3/09 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Drawing

5. The drawings/figures stand objected to because sequence listings included in the specification must not be duplicated in the drawings. See 37 C.F.R. §1.58(a) and §1.83. On p. 4 of the response, Applicant request that the objection be held in

abeyance until the instant application is in a condition for allowance. The objection to figures/drawings is maintained of record until the correction is made. See MPEP 608.02 [R-3]-I Drawing requirements

If the specification includes a sequence listing or a table, such a sequence listing or table is not permitted to be reprinted in the drawings. 37 CFR 1.83(a) and 1.58(a).

Claim Rejections/Objections Withdrawn

6. The objection of claim 17 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is moot because the claim is canceled.

Claim Rejections/Objections Maintained

In view of the amendment filed on 7/3/09, the following rejections are maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 8, 11, and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,674,711 in view of US2003144189, US 6,632,637, US 6,136,536, US20030083242, US 6,852,510 and further in view of Logan et al. (Proc. Natl. Acad. Sci. USA, 1984, 81:3655-3659) and WO03/048366. The rejection is maintained for the reasons made of record.

Claims 1, 8, 11, and 13 as amended are drawn to an expression vector, a transformant and a method of making human FSH protein wherein the expression vector comprises a gene encoding human FSH consisting of human FSH beta subunit gene having the sequence of SEQ ID NO2, internal ribosomal entry site (IRES) sequence having the sequence of SEQ ID NO:7, and human FSH alpha subunit gene having the sequence of SEQ ID NO:1, sequentially in 5'-3' direction; a promoter sequence of early gene of CMV having the sequence of SEQ ID NO:8; a tripartite leader sequence of adenovirus having the sequence of SEQ ID NO:9; a polyadenylation motif sequence of early gene of SV40 virus having the sequence of SEQ ID NO:13 and/or a polyadenylation motif sequence of bovine growth hormone (BGH) gene having the sequence of SEQ ID NO:14 and a dihydrofolate reductase (DHFR) gene having the sequence of SEQ ID NO:12, wherein the vector expresses FSH beta and alpha subunits that form a glycosylated FSH heterodimer.

On p. 4 of the response, Applicant argues that the rejection is non-obvious and week because eight references were cited to formulate the 103 rejection. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). In addition, in this case, the claimed sequences with a nucleotide mutation that does not change the expression of the protein are obvious over the cited references because the encoded amino acid sequences are the same. Even there is an amino acid change that is conserved does not change the activity of the claimed molecule. Thus, the minor difference in an amino acid residue or nucleotide in the recited sequences does not render the claimed invention novel or inventive because the encoded human FSH beta and alpha subunits still have the same activity. Furthermore, the function, the sequences and the use of the cited early gene sequences of CMV, SV40 and the sequences of polyA and DHFR are well known in the art.

On p. 5 of the response, Applicant argues that there is no reasonable expectation of success to reach the claimed invention. Applicant argues that the '637 patent does not teach or suggest the use of IRES sequence for the expression of structural gene such as human FSH gene. Applicant argues that although the '637 patent discloses an expression vector that expresses at least two exogenous genes separated by IRES, the

second coding sequences are selectable markers and the expression levels of the second sequences were not measured relative to the first gene expression. In addition, Applicant argues that the '637 patent fails to teach the claimed construct (FSHbeta)(IRES)(FSHalpha). Applicant argues that the '711 patent discloses full biological activity of human FSH requires on to one stoichiometery of the alpha and beta subunits. Applicant acknowledges that it is obvious to try to express the full FSH protein using (FSHbeta)(IRES)(FSHalpha) but the '637 patent fails to provide evidence that a one-to-one expression of each of the two subunit polypeptides was produced by from the vector. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, US 5,674,711 (the '711 patent) teaches a recombinant transformant for producing human FSH comprising an expression vector (CLH3AXSV2) comprising a gene encoding human FSH alpha or beta, a promoter sequence (a mouse metallothionein-I (MT-1) promoter), a polyadenylation (polyA) motif sequence (a SV40 early polyA motif) and a dihydrofolate reductase (DHFR) gene (a mouse DHFR gene)) (see cols. 3-13; figure 4; examples 1-6, in particular). Although the '711 patent does not explicitly teaches SEQ ID NOs:1 & 2 encoding human FSH alpha and beta subunits

respectively, the amino acid sequences of human FSH alpha and beta subunits are disclosed by US2003144189. US2003144189 teaches a DNA sequence having 99.5% identity to instant SEQ ID NO:1 to encode human FSH alpha subunit and a DNA sequence having 98.8% identity to instant SEQ ID NO:2 to encode human FSH alpha subunit. The translated amino acid sequence of human alpha subunit in US2003144189 is identical to the amino acid sequence encoded by instant SEQ ID NO:1. Although there is one-amino acid mismatch (cysteine vs valine) in the human FSH beta subunit of US2003144189, the FSH of the instant application is expected to have the same activity as that of US2003144189 because cysteine and valine residues are conserved amino acids to each other and thus would not change the activity of FSH.

Although the '711 patent does not explicitly teach SEQ ID NO:13 as a polyA motif sequence, the sequence of a polyA motif in the early gene of SV40 virus is known in the art as evidenced by US 6,632,637. In addition, the '711 patent teaches that FSH functions as a dimer containing FSH alpha and beta subunits (see col.1, lines 33-65, in particular). The '711 patent also teaches co-expression human FSH alpha and beta subunits by co-transfecting an expression vector containing a FSH alpha subunit gene and an expression vector containing a FSH beta subunit gene in CHO/DHFR- cells (see cols. 2-4, examples 1-2; col.14-16, claims 1-16, in particular). The '711 patent teaches a method of making human FSH protein (related to clams 11 and 13) (see col.4, line 32-col.6, line 21; examples 1-6, in particular). Thus, it is obvious to simultaneously express both human beta and alpha subunit to form a functional dimer.

Although the '711 patent does not teach an IRES sequence in an expression vector, US Patent No. 6,632,637 (the '637 patent) teaches an expression vector that can express at least two exogenous genes wherein the two exogenous genes are separated by an internal ribosomal entry site (col.1, line 38-col.2, line 63). The '637 patent teaches a method of making protein (related to claims 11 and 13) and a transformant of DHFR- CHO cell line (related to claim 8) containing an expression vector (related claim 1) containing an a CMV promoter, an IL4R gene, an IRES, a DHFR gene and a SV40 polyA sequence (instant SEQ ID NO:13) and a polyA sequence of BGH (instant SEQ ID NO:14) (see figure 1; col.2, line 13-col.6. line 35; col.6 table1; col. 29-32, claims 1-44; col.7, line 1-col.9, line 55, in particular). Thus, regardless of whether the efficiency of expression between the first gene and second gene separated by IRES is known or not, the combined teachings of the '711 patent and the '637 patent provide an expectation of success to simultaneously express both human beta and alpha subunit genes in a construct containing IRES and also provide a motivation to express both human beta and alpha subunit together because a functional human FSH requires both alpha and beta subunits to form a dimer.

Although the '637 patent does not explicitly teach instant SEQ ID NO:7 as a DNA sequence for IRES, US patent No. 6,852,510 (the '510 patent) teaches a DNA sequence of IRES having a DNA sequence 97% identical to instant SEQ ID NO:7. The N-terminus of the IRES DNA sequence of the '510 patent is different from that of the instant SEQ ID NO:7 with a 10-nucleotide mismatch. These 10 nucleotides are for different restriction enzyme sites and are not essential for ribosomal entry because both

IRES DNA sequences have the same function for internal ribosomal entry. Although the '637 and '510 patent do not explicitly teach the DNA sequence for a CMV promoter, US20030083242 teaches a CMV promoter having a DNA sequence 99.3% identical to instant SEQ ID NO:8. The 3-nucleotide mismatch to instant SEQ ID NO:8 at the C-terminus as disclosed by US20030083242 is not essential because both of the CMV sequence have the same function to serve as a promoter.

Although the '711 patent does not explicitly teach SEQ ID NO:12 as a sequence for a DHFR gene as recited in instant claims, US 6,136,536 teaches the DNA sequence of DHFR (instant SEQ ID NO:12). Although the '711 patent does not teach SEQ ID NO:9 for a tripartite leader sequence of adenovirus, WO03/048366 teaches that an adenovirus tripartite leader sequence having 100% identity to instant SEQ ID NO:9 and Logan et al. teach that an adenovirus tripartite leader sequence can enhance translation of mRNA (see p. 3655, abstract; p. 3656, 2nd col., 4th paragraph, in particular).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to combine the teachings of US5,674,711, US2003144189, US6,632,637, US 6,136,536, US20030083242, US6,852,510, Logan et al. (Proc. Natl. Acad. Sci. USA, 1984, 81:3655-3659) and WO03/048366 to generate an expression vector to express a glycosylated FSH heterodimer. The skilled artisan would have been motivated to do so with an expectation of success because the '711 patent teaches a functional FSH requires both of alpha and a beta FSH subunits, and the '637 patents teach a method of making proteins using a transformant of DHFR- CHO cell line containing an expression vector that contains a CMV promoter, an IRES, a DHFR gene

and a SV40 polyA sequence and a polyA sequence of BGH to express two different proteins simultaneously. In addition, the claimed invention is obvious over the applied references and is expected to generate a glycosylated FSH heterodimer because US2003144189 teaches the DNA sequences of SEQ ID NOs: 1 and 2 for human FSH alpha and beta subunits, the '510 patent teaches the DNA sequence of SEQ ID NO:7 for IRES, US20030083242 teaches the DNA sequence of SEQ ID NO:8 for a CMV promoter, the '637 patent teaches the DNA sequences of SEQ ID NO:13 and 14 for SV40 and BGH poly-A motifs, the '536 patent teaches the DNA sequence of SEQ ID NO: 12 for DHFR, WO03/048366 teaches the DNA sequence of SEQ ID NO:9 for an adenovirus tripartite leader sequence and Logan teaches that an adenovirus tripartite leader sequence can enhance translation of mRNA.

Note that

The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

In this case, the instant claims are obvious over the cited references because all the claimed elements were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods to yield predictable results or to use these known technique to improve similar products in the same way.

On p. 6 of the response, Applicant argues that Mizuguchi et al. (Mol. Therapy. 2000. 1:376-382) teach away from the claimed invention because Mizuguchi discloses that the expression of the IRES-dependent second gene was less efficient than that of the first gene. Applicant argues that based on the teaching of Mizuguchi, a skilled

artisan would not make the (FSHbeta)(IRES)(FSHalpha) construct to express FSH protein. Applicant argues that it is not obvious to the teachings of the cited references. Applicant's arguments have been fully considered but they are not persuasive.

In response, note that Mizuguchi is not cited as a prior art and thus is not relevant to the instant rejection. Although Mizuguchi describes the expression level of the IRES-dependent second gene is less efficient, the teaching of Mizuguchi does not teach away from the invention. In contrast, the teaching of Mizuguchi provides an expectation of success to express both exogenous genes in a construct separated by an IRES and is consistent with the combined teachings of the cited references.

On p. 7 of the response, Applicant argues that Applicant have a unexpectedly successfully produced fully functional human gene product in adequate amounts for further use by using the claimed method containing the IRES sequence. Applicant argues that the claimed construct is designed to maximize the expression of human FSH that requires the one to one stoichometry of an alpha and a beta subunit binding. Applicant argues that the claimed invention is free of prior art and is not obvious over the cited references and further cites allowed claims of the priority Korean patent application (Korean patent registration no. 10-0533734) and the first office action of European patent application in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In response, although the prosecution history and decision of the international applications serve as references for US applications, the prosecution and the

examination decision of the US applications are not bound by the decision of international partner applications. Each patent application is by its own merits and is judged independently.

In this case, the examiner asserts that the cited references render the claimed invention obvious because the '711 patent teaches a method of making human FSH protein as in clams 11 and 13 (see col.4, line 32-col.6, line 21; examples 1-6, in particular) and co-expressing human FSH alpha and beta subunits by co-transfecting an expression vector containing a FSH alpha subunit gene and an expression vector containing a FSH beta subunit gene in CHO/DHFR- cells (see cols. 2-4, examples 1-2; col.14-16, claims 1-16, in particular). Although the '711 patent does not teach an IRES sequence in an expression vector, US Patent No. 6,632,637 (the '637 patent) teaches an expression vector that can express at least two exogenous genes wherein the two exogenous genes are separated by an internal ribosomal entry site (col.1, line 38-col.2, line 63). Thus, it is obvious to make a construct to express both human alpha and beta subunits simultaneously in a construct containing IRES using a construct containing IRES, and other early genes of CMV, polyA, SV40 and DHFR to generate a glycosylated FSH heterodimer.

In addition, the result of the use of a construct to express both of the FSH subunits is expected based on the combined teachings of the cited references. Note that

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). See MPEP 716.02(a)-I.

In this case, Applicants allegedly argues that the claimed construct has unexpected results over the prior art. In contrast, Applicant fails to provide evidence of side-by-side comparisons to demonstrate unexpected results as claimed. No comparative data shows the unexpected results derived from the claimed construct as recited in instant claim 1 versus those of the combined reference teachings.

"Evidence of unexpected results must be weighed against evidence supporting *prima facie* obviousness in making a final determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978)." See MPEP 716.02(c)-I.

Since Applicant fails to provide any evidence as discussed above to support any unexpected results as claimed, the claimed construct is obvious over the prior art, absent evidence to the contrary.

Conclusion

Allowable Subject Matter

8. Claim 10 is objected to as being dependent upon a rejected base claim 1, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. Claims 1, 8, 11 and 13 are rejected.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with

the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chang-Yu Wang, Ph.D.
August 27, 2009

/Chang-Yu Wang/
Examiner, Art Unit 1649